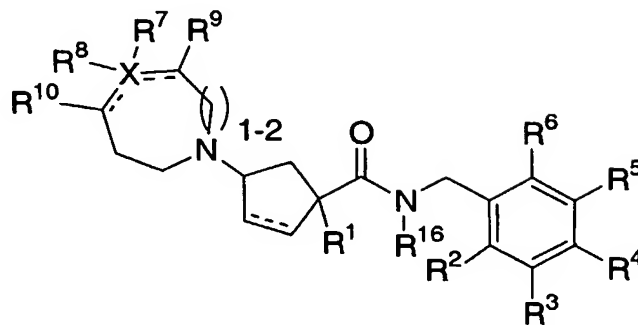


## WHAT IS CLAIMED IS:

1. A compound of the formula I:



I

wherein:

X is O, N, S, SO<sub>2</sub> or C;

R<sup>1</sup> is selected from:

hydrogen, -C<sub>1-6</sub>alkyl, -C<sub>0-6</sub>alkyl-O-C<sub>1-6</sub>alkyl, -C<sub>0-6</sub>alkyl-S-C<sub>1-6</sub>alkyl, -(C<sub>0-6</sub>alkyl)-(C<sub>3-7</sub>cycloalkyl)-(C<sub>0-6</sub>alkyl), hydroxy, heterocycle, -CN, -NR<sup>12</sup>R<sup>12</sup>, -N R<sup>12</sup>COR<sup>13</sup>, -N R<sup>12</sup>SO<sub>2</sub>R<sup>14</sup>, -N R<sup>12</sup>SO<sub>2</sub>NR<sup>12</sup> R<sup>12</sup>-, -COR<sup>11</sup>, -CON R<sup>12</sup> R<sup>12</sup>, and phenyl, where:

said alkyls and cycloalkyls are unsubstituted or substituted with 1-7 substituents independently selected from: halo, hydroxy, -O-C<sub>1-3</sub>alkyl, trifluoromethyl, C<sub>1-3</sub>alkyl, -O-C<sub>1-3</sub>alkyl, -COR<sup>11</sup>, -SO<sub>2</sub>R<sup>14</sup>, -NHCOCH<sub>3</sub>, -NHCO<sub>2</sub>CH<sub>3</sub>, -heterocycle, =O, and -CN,

said phenyl and heterocycle are unsubstituted or substituted with 1-3 substituents independently selected from: halo, hydroxy, C<sub>1-3</sub>alkyl, C<sub>1-3</sub>alkoxy and trifluoromethyl;

R<sup>11</sup> is selected from: hydroxy, hydrogen, C<sub>1-6</sub> alkyl, -O- C<sub>1-6</sub>alkyl, benzyl, phenyl, C<sub>3-6</sub> cycloalkyl, where the alkyl, phenyl, benzyl, and cycloalkyl groups are unsubstituted or substituted with 1-3 substituents independently selected from: halo, hydroxy, C<sub>1-3</sub>alkyl, C<sub>1-3</sub>alkoxy, -CO<sub>2</sub>H, -CO<sub>2</sub>-C<sub>1-6</sub> alkyl, and trifluoromethyl,

R<sup>12</sup> is independently selected from: hydrogen, C<sub>1-6</sub> alkyl, benzyl, phenyl, C<sub>3-6</sub> cycloalkyl, where the alkyl, phenyl, benzyl, and cycloalkyl groups are unsubstituted or substituted with 1-3 substituents independently selected from: halo, hydroxy, C<sub>1-3</sub>alkyl, C<sub>1-3</sub>alkoxy, -CO<sub>2</sub>H, -CO<sub>2</sub>-C<sub>1-6</sub> alkyl, and trifluoromethyl,

R<sup>13</sup> is selected from: hydrogen, C<sub>1-6</sub> alkyl, -O-C<sub>1-6</sub>alkyl, benzyl, phenyl, C<sub>3-6</sub> cycloalkyl, where the alkyl, phenyl, benzyl, and cycloalkyl groups are unsubstituted or substituted with 1-3 substituents independently selected from: halo, hydroxy, C<sub>1-3</sub>alkyl, C<sub>1-3</sub>alkoxy, -CO<sub>2</sub>H, -CO<sub>2</sub>-C<sub>1-6</sub> alkyl, and trifluoromethyl, and

R<sup>14</sup> is selected from: hydroxy, C<sub>1-6</sub> alkyl, -O-C<sub>1-6</sub>alkyl, benzyl, phenyl, C<sub>3-6</sub> cycloalkyl where the alkyl, phenyl, benzyl, and cycloalkyl groups can be unsubstituted or substituted with 1-3 independently selected from: halo, hydroxy, C<sub>1-3</sub>alkyl, C<sub>1-3</sub>alkoxy, -CO<sub>2</sub>H, -CO<sub>2</sub>-C<sub>1-6</sub> alkyl, and trifluoromethyl;

R<sup>2</sup> is selected from:

- (a) hydrogen,
- (b) C<sub>1-3</sub>alkyl, unsubstituted or substituted with 1-3 fluoro,
- (c) -O-C<sub>1-3</sub>alkyl, unsubstituted or substituted with 1-3 fluoro,
- (d) hydroxy,
- (e) chloro,
- (f) fluoro,
- (g) bromo, and
- (h) phenyl;

R<sup>3</sup> is selected from:

- (a) hydrogen,
- (b) hydroxy,
- (c) halo,
- (d) C<sub>1-3</sub>alkyl unsubstituted or substituted with 1-6 substituents independently selected from: fluoro, hydroxy, and -COR<sup>11</sup>,
- (e) -NR<sup>12</sup>R<sup>12</sup>,
- (f) -COR<sup>11</sup>,
- (g) -CONR<sup>12</sup>R<sup>12</sup>,
- (h) -NR<sup>12</sup>COR<sup>13</sup>,
- (i) -OCONR<sup>12</sup>R<sup>12</sup>,
- (j) -NR<sup>12</sup>CONR<sup>12</sup>R<sup>12</sup>,
- (k) -heterocycle,
- (l) -CN,

- (m) -NR<sup>12</sup>-SO<sub>2</sub>-NR<sup>12</sup>R<sup>12</sup>,
- (n) -NR<sup>12</sup>-SO<sub>2</sub>-R<sup>14</sup>,
- (o) -SO<sub>2</sub>-NR<sup>12</sup>R<sup>12</sup> and
- (p) nitro;

5

R<sup>4</sup> is selected from:

- (a) hydrogen,
- (b) C<sub>1-3</sub>alkyl, unsubstituted or substituted with 1-3 fluoro,
- 10 (c) -O-C<sub>1-3</sub>alkyl, unsubstituted or substituted with 1-3 fluoro,
- (d) hydroxy,
- (e) chloro,
- (f) fluoro,
- (g) bromo, and
- 15 (h) phenyl;

R<sup>5</sup> is selected from:

- (a) C<sub>1-6</sub>alkyl, unsubstituted or substituted with 1-6 fluoro, hydroxyl, or both,
- 20 (b) -O-C<sub>1-6</sub>alkyl, unsubstituted or substituted with 1-6 fluoro,
- (c) -CO-C<sub>1-6</sub>alkyl, unsubstituted or substituted with 1-6 fluoro,
- (d) -S-C<sub>1-6</sub>alkyl, unsubstituted or substituted with 1-6 fluoro,
- (e) -pyridyl, unsubstituted or substituted with one or more substituents
- 25 selected from: halo, trifluoromethyl, C<sub>1-4</sub>alkyl, and COR<sup>11</sup>,
- (f) fluoro,
- (g) chloro,
- (h) bromo,
- (i) -C<sub>4-6</sub>cycloalkyl, unsubstituted or substituted with 1-6 fluoro,
- (j) -O-C<sub>4-6</sub>cycloalkyl, unsubstituted or substituted with 1-6 fluoro,
- 30 (k) phenyl, unsubstituted or substituted with one or more substituents selected from: halo, trifluoromethyl, C<sub>1-4</sub>alkyl, and COR<sup>11</sup>,
- (l) -O-phenyl, unsubstituted or substituted with one or more substituents
- 35 selected from: halo, trifluoromethyl, C<sub>1-4</sub>alkyl, and COR<sup>11</sup>,
- (m) -heterocycle,
- (n) -CN, and
- (o) -COR<sup>11</sup>;

R<sup>6</sup> is selected from:

- 40 (a) hydrogen,
- (b) C<sub>1-3</sub>alkyl, unsubstituted or substituted with 1-3 fluoro,
- (c) -O-C<sub>1-3</sub>alkyl, unsubstituted or substituted with 1-3 fluoro,

- 5 (d) hydroxy,  
 (e) chloro,  
 (f) fluoro,  
 (g) bromo, and  
 (h) phenyl;

$R^7$  is selected from:

- 10 (a) hydrogen,  
 (b) (C<sub>0-6</sub>alkyl)-phenyl,  
 (c) (C<sub>0-6</sub>alkyl)-heterocycle,  
 (d) (C<sub>0-6</sub>alkyl)-C<sub>3-7</sub>cycloalkyl,  
 (e) (C<sub>0-6</sub>alkyl)-COR<sup>11</sup>,  
 (f) (C<sub>0-6</sub>alkyl)-(alkene)-COR<sup>11</sup>,  
 15 (g) (C<sub>0-6</sub>alkyl)-SO<sub>3</sub>H,  
 (h) (C<sub>0-6</sub>alkyl)-W-C<sub>0-4</sub>alkyl, where W is selected from: a single bond, - O-, -S-,  
 , -SO-, -SO<sub>2</sub>-, -CO-, -CO<sub>2</sub>-, -CONR<sup>12</sup>- and -NR<sup>12</sup>-,  
 (i) (C<sub>0-6</sub>alkyl)-CON R<sup>12</sup>-phenyl,  
 (j) (C<sub>0-6</sub>alkyl)-CON R<sup>15</sup>-V-CO R<sup>11</sup>, where V is selected from C<sub>1-6</sub>alkyl or  
 20 phenyl, and  
 (k) nothing, when X is O, S, or SO<sub>2</sub>,

where:

- 25 R<sup>15</sup> is hydrogen or C<sub>1-4</sub>alkyl, or where R<sup>15</sup> is joined via a 1-5 carbon tether to one of the carbons of V to form a ring,

C<sub>0-6</sub>alkyl is unsubstituted or substituted with 1-5 substituents, where the substituents are independently selected from:

- 30 (a) halo,  
 (b) hydroxy,  
 (c) -C<sub>0-6</sub>alkyl  
 (d) -O-C<sub>1-3</sub>alkyl,  
 35 (e) trifluoromethyl, and  
 (f) -C<sub>0-2</sub>alkyl-phenyl,

phenyl, heterocycle, cycloalkyl, and C<sub>0-4</sub>alkyl is unsubstituted or substituted with 1-5 substituents where the substituents are independently selected from:

- 40 (a) halo,  
 (b) trifluoromethyl,  
 (c) hydroxy,

- (d) C<sub>1-3</sub>alkyl,
- (e) -O-C<sub>1-3</sub> alkyl,
- (f) -C<sub>0-3</sub>-COR<sup>11</sup>,
- (g) -CN,
- (h) -NR<sup>12</sup>R<sup>12</sup>,
- (i) -CONR<sup>12</sup>R<sup>12</sup>, and
- (j) -C<sub>0-3</sub>-heterocycle,

where the phenyl and heterocycle may be fused to another heterocycle, which itself may be unsubstituted or substituted with 1-2 substituents independently selected from hydroxy, halo, -CO R<sup>11</sup>, and -C<sub>1-3</sub>alkyl, and where

alkene is unsubstituted or substituted with 1-3 substituents which are independently selected from:

- (a) halo,
- (b) trifluoromethyl,
- (c) C<sub>1-3</sub>alkyl,
- (d) phenyl, and
- (e) heterocycle;

R<sup>8</sup> is selected from:

- (a) hydrogen,
- (b) nothing when X is either O, S, SO<sub>2</sub> or N or when a double bond joins the carbons to which R<sup>7</sup> and R<sup>10</sup> are attached,
- (c) hydroxy,
- (d) C<sub>1-6</sub>alkyl,
- (e) C<sub>1-6</sub>alkyl-hydroxy,
- (f) -O-C<sub>1-3</sub>alkyl,
- (g) -COR<sup>11</sup>,
- (h) -CONR<sup>12</sup>R<sup>12</sup>, and
- (i) -CN;

or where R<sup>7</sup> and R<sup>8</sup> may be joined together to form a ring which is selected from:

- (a) 1H-indene,
- (b) 2,3-dihydro-1H-indene,
- (c) 2,3-dihydro-benzofuran,
- (d) 1,3-dihydro-isobenzofuran,
- (e) 2,3-dihydro-benzothiofuran,
- (f) 1,3-dihydro-isobenzothiofuran,
- (g) 6H-cyclopenta[d]isoxazol-3-ol

- (h) cyclopentane, and
- (i) cyclohexane,

where the ring formed may be unsubstituted or substituted with 1-5 substituents independently selected from:

- (a) halo,
- (b) trifluoromethyl,
- (c) hydroxy,
- (d) C<sub>1-3</sub>alkyl,
- (e) -O-C<sub>1-3</sub>alkyl,
- (f) -C<sub>0-3</sub>-COR<sup>11</sup>,
- (g) -CN,
- (h) -NR<sup>12</sup>R<sup>12</sup>,
- (i) -CONR<sup>12</sup>R<sup>12</sup>, and
- (j) -C<sub>0-3</sub>-heterocycle;

or where R<sup>7</sup> and R<sup>9</sup> or R<sup>8</sup> and R<sup>10</sup> may be joined together to form a ring which is phenyl or heterocycle, wherein the ring is unsubstituted or substituted with 1-7 substituents independently selected from:

- (a) halo,
- (b) trifluoromethyl,
- (c) hydroxy,
- (d) C<sub>1-3</sub>alkyl,
- (e) -O-C<sub>1-3</sub>alkyl,
- (f) -COR<sup>11</sup>,
- (g) -CN,
- (h) -NR<sup>12</sup>R<sup>12</sup>, and
- (i) -CONR<sup>12</sup>R<sup>12</sup>;

R<sup>9</sup> and R<sup>10</sup> are independently selected from:

- (a) hydrogen,
- (b) hydroxy,
- (c) C<sub>1-6</sub>alkyl,
- (d) C<sub>1-6</sub>alkyl-COR<sup>11</sup>,
- (e) C<sub>1-6</sub>alkyl-hydroxy,
- (f) -O-C<sub>1-3</sub>alkyl,
- (g) =O, when R<sup>9</sup> or R<sup>10</sup> is connected to the ring via a double bond
- (h) halo;

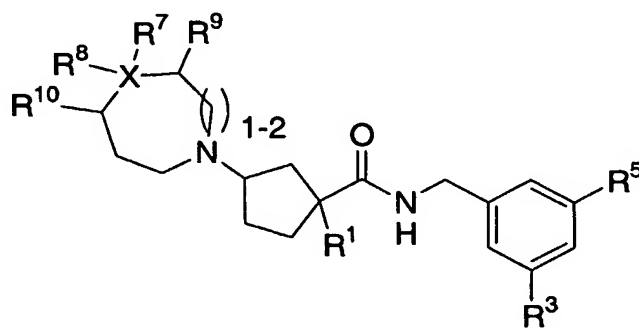
R<sup>16</sup> selected from:

- (a) hydrogen,  
 (b) phenyl,  
 5 (c) C<sub>1-6</sub>alkyl which may be substituted or unsubstituted with 1-6 of the following substituents: -COR<sup>11</sup>, hydroxy, fluoro, chloro, -O-C<sub>1-3</sub> alkyl;

the dashed line represents a single or a double bond;

10 and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

2. A compound of Claim 1 of formula Ia:

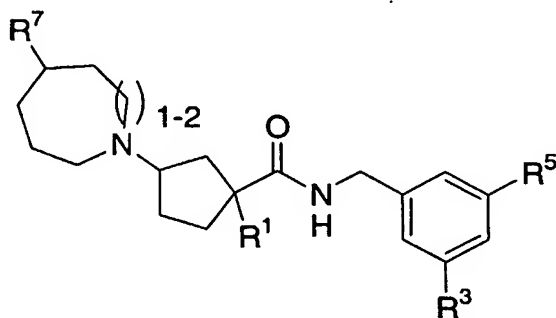


15

Ia

and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

3. A compound of Claim 1 of formula Ib:

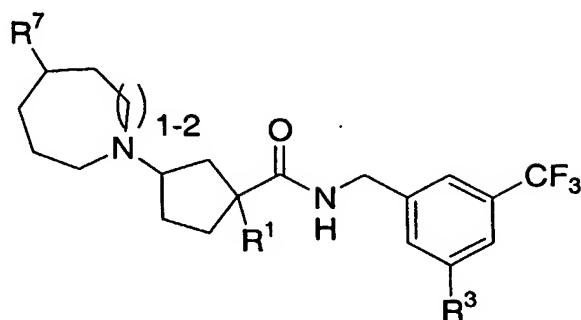


20

Ib

and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

4. A compound of Claim 1 of formula Ic:



Ic

5 and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

5. The compound of claim 1, wherein X is N, O, or C.

6. The compound of claim 1, wherein R<sup>1</sup> is selected from -C<sub>1-6</sub>alkyl, -C<sub>0-6</sub>alkyl-O-C<sub>1-6</sub>alkyl, heterocycle, and -(C<sub>0-6</sub>alkyl)-(C<sub>3-7</sub>cycloalkyl)-(C<sub>0-6</sub>alkyl),

where the alkyl, heterocycle, and the cycloalkyl are unsubstituted or substituted with 1-7 substituents independently selected from:

- (a) halo,
- (b) hydroxy,
- (c) -O-C<sub>1-3</sub>alkyl,
- (d) trifluoromethyl,
- (f) C<sub>1-3</sub>alkyl,
- (g) -O-C<sub>1-3</sub>alkyl,
- (h) -COR<sup>11</sup>,
- (i) -CN,
- (j) -NR<sup>12</sup>R<sup>12</sup>,
- (k) -CONR<sup>12</sup>R<sup>12</sup>, and
- (j) -NCOR<sup>13</sup>.

7. The compound of claim 1, wherein R<sup>1</sup> is:

-C<sub>1-6</sub>alkyl, unsubstituted or substituted with 1-6 substituents independently selected from:

- (a) halo,
- (b) hydroxy,
- (c) -O-C<sub>1-3</sub>alkyl,
- (d) trifluoromethyl, and



(e)  $-\text{COR}^{11}$ ;

$-\text{C}_0\text{-6alkyl-O-C}_1\text{-6alkyl-}$ , which is unsubstituted or substituted with 1-6 substituents independently selected from:

- (a) halo,  
(b) trifluoromethyl, and  
(c)  $-\text{COR}^{11}$ ;

$-(\text{C}_3\text{-5cycloalkyl})-(\text{C}_0\text{-6alkyl})$ , which is unsubstituted or substituted with 1-7 substituents independently selected from:

- (a) halo,  
(b) hydroxy,  
(c)  $-\text{O-C}_1\text{-3alkyl}$ ,  
(d) trifluoromethyl, and  
(e)  $-\text{COR}^{11}$ ; and

heterocycle, unsubstituted or substituted with  $-\text{NCOR}^{13}$  or  $-\text{NR}^{12}\text{R}^{12}$ .

8. The compound of claim 1, wherein  $\text{R}^1$  is selected from:

- (a)  $\text{C}_1\text{-6alkyl}$ ,  
(b)  $\text{C}_1\text{-6alkyl}$  substituted with hydroxy,  
(c)  $\text{C}_1\text{-6alkyl}$  substituted with 1-6 fluoro, and  
(d) thiazole, unsubstituted or substituted with  $-\text{NHCOR}^{13}$ .

9. The compound of claim 1, wherein  $\text{R}^1$  is selected from:

- (a)  $-\text{CH}(\text{CH}_3)_2$ ,  
(b)  $-\text{C}(\text{OH})(\text{CH}_3)_2$ ,  
(c)  $-\text{CH}(\text{OH})\text{CH}_3$ ,  
(d)  $-\text{CH}_2\text{CF}_3$ , and  
(e) -thiazole, bonded to the core at the 4 position of the thiazole ring, unsubstituted or substituted with  $-\text{NHCOCH}_3$  at the 2 position of the thiazole ring.

10. The compound of claim 1, wherein  $\text{R}^2$  is hydrogen.

11. The compound of claim 1, wherein  $\text{R}^3$  is selected from:

- (a) hydrogen,  
(b) halo,  
(c) hydroxy,  
(d)  $\text{C}_1\text{-3alkyl}$ , where the alkyl is unsubstituted or substituted with 1-6 substituents independently selected from: fluoro, and hydroxy,

- (e) -COR<sup>11</sup>,
- (f) -CONR<sup>12</sup>R<sup>12</sup>,
- (g) -heterocycle,
- (h) -NR<sup>12</sup>-SO<sub>2</sub>-NR<sup>12</sup>R<sup>12</sup>,
- (i) -NR<sup>12</sup>-SO<sub>2</sub>-R<sup>14</sup>,
- (j) -SO<sub>2</sub>-NR<sup>12</sup>R<sup>12</sup>,
- (k) -nitro, and
- (l) -NR<sup>12</sup>R<sup>12</sup>.

12. The compound of claim 1, wherein R<sup>3</sup> is selected from:

- (a) hydrogen,
- (b) fluoro, and
- (c) trifluoromethyl.

13. The compound of claim 1, R<sup>3</sup> is selected from fluoro and trifluoromethyl.

14. The compound of claim 1, wherein R<sup>4</sup> is hydrogen.

15. The compound of claim 1, wherein R<sup>5</sup> is selected from:

- (a) C<sub>1-6</sub>alkyl substituted with 1-6 fluoro,
- (b) -O-C<sub>1-6</sub>alkyl substituted with 1-6 fluoro,
- (c) chloro,
- (d) bromo, and
- (e) phenyl.

16. The compound of claim 1, wherein R<sup>5</sup> is selected from:

- (a) trifluoromethyl,
- (b) trifluoromethoxy,
- (c) chloro,
- (d) bromo, and
- (e) phenyl.

17. The compound of claim 1, wherein R<sup>5</sup> is trifluoromethyl.

18. The compound of claim 1, wherein R<sup>6</sup> is hydrogen.

19. The compound of claim 1, wherein R<sup>7</sup> is selected from phenyl, heterocycle, C<sub>3-7</sub>cycloalkyl, C<sub>1-6</sub>alkyl, -COR<sup>11</sup>, and -CONH-V-COR<sup>11</sup>,

where V is selected from C<sub>1-6</sub>alkyl or phenyl, and

where the phenyl, heterocycle, C<sub>3-7</sub>cycloalkyl, and C<sub>1-6</sub>alkyl is unsubstituted or substituted with 1-5 substituents independently selected from:

- 5 (a) halo,
- (b) trifluoromethyl,
- (c) hydroxy,
- (d) C<sub>1-3</sub>alkyl,
- (e) -O-C<sub>1-3</sub>alkyl,
- 10 (f) -COR<sup>11</sup>,
- (g) -CN,
- (h) -heterocycle, and
- (i) -CONR<sup>12</sup>R<sup>12</sup>.

15 20. The compound of claim 1, wherein R<sup>7</sup> is selected from phenyl, heterocycle, C<sub>1-4</sub>alkyl, -COR<sup>11</sup>, and -CONH-V-COR<sup>11</sup>,

where V is selected from C<sub>1-6</sub>alkyl or phenyl, and

20 where the phenyl, heterocycle, and C<sub>1-4</sub>alkyl is unsubstituted or substituted with 1-3 substituents independently selected from:

- (a) halo,
- (b) hydroxy,
- 25 (c) C<sub>1-3</sub>alkyl,
- (d) -O-C<sub>1-3</sub>alkyl,
- (e) -COR<sup>11</sup>, and
- (f) -heterocycle.

30 21. The compound of claim 1, wherein R<sup>7</sup> is selected from:

- (a) hydrogen,
- (b) -COR<sup>11</sup>,
- (c) -CONHCH<sub>3</sub>,
- 35 (d) phenyl,
- (e) heterocycle,

22. The compound of claim 1, wherein when X is C, R<sup>8</sup> is selected from:

- 40 (a) hydrogen,
- (b) hydroxy,
- (c) -CN, and
- (d) -F.

45 23. The compound of claim 1, wherein R<sup>8</sup> is hydrogen.

24. The compound of claim 1, wherein  $R^7$  and  $R^8$  may be joined together to form a ring which is selected from 1H-indene and 2,3-dihydro-1H-indene,

5 where the ring formed may be unsubstituted or substituted with 1-3 substituents independently selected from:

- (a) halo,
- (b) hydroxy,
- 10 (c)  $C_{1-3}$ alkyl,
- (d)  $-O-C_{1-3}$ alkyl,
- (e)  $-COR^{11}$ , and
- (f) -heterocycle.

15 25. The compound of claim 1, wherein  $R^9$  and  $R^{10}$  are independently selected from:

- (a) hydrogen,
- (b) hydroxy,
- 20 (c)  $-CH_3$ ,
- (d)  $-O-CH_3$ , and
- (e)  $=O$ , where  $R^9$  and/or  $R^{10}$  are joined to the ring via a double bond.

25 26. The compound of claim 1, wherein  $R^9$  and  $R^{10}$  are hydrogen.

27. The compound of claim 1, wherein  $R^{16}$  is hydrogen.

28. A pharmaceutical composition which comprises an inert carrier and a compound of Claim 1.

30 29. A method for modulation of chemokine receptor activity in a mammal which comprises the administration of an effective amount of a compound of Claim 1.

35 30. A method for treating, ameliorating, controlling or reducing the risk of an inflammatory and immunoregulatory disorder or disease which comprises the administration to a patient of an effective amount of a compound of Claim 1.

40 31. A method for treating, ameliorating, controlling or reducing the risk of rheumatoid arthritis which comprises the administration to a patient of an effective amount of a compound of Claim 1.